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(ii) an organic solvent; and

(ii) a propellant.

REMARKS

Claims 19-46 are pending in this application. Applicants acknowledge the renumbering of claims 32 and higher as indicated by the Examiner on page 2 of paper No.8. In lieu of filing a Brief on Appeal, Applicant submits herewith a Continued Prosecution Application (CPA) Request including a Request for a Four Month Extension of Time. The pending claims are rejected under 35 U.S.C. §102(b) and under 35 U.S.C. §103. Applicants have amended the claims to encompass non-encapsulated cyclosporine. The subject matter of the amended claims is fully supported in the specification and claims as originally filed. For reasons set forth below, Applicants request that the rejections be withdrawn and the pending claims allowed to issue.

1. The Claims Are Not Anticipated

Claims 19, 21, 25, 28, 30, 32, 35, 37, 38, 40, 41, 44, 46, and 47 are rejected under 35 U.S.C. § 102(b) as being anticipated by Gilbert et. al (1993, Transplantation 56: 974-7; "Gilbert"). Claims 20, 26, 28, 30, 31, 35, 36, 38, 39, 41, 43, 44, and 46-47 are rejected under 35 U.S.C. § 102(b) as being anticipated by Knight et al. or Waldrep et al. These rejections are in error and should be withdrawn for the reasons set forth below.

Anticipation requires that all the elements and limitations of the claims be found

within a single prior art references. There must be no difference between the claimed invention and the reference disclosures, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 927 F.2d 1565, 18 U.S.P.Q.2d 1001, 18 U.S.P.Q.2d 1896 (Fed. Cir. 1991). Further, the use of the claim phrase "consisting essentially of " excludes ingredients that would materially effect the basic and novel characteristics of the claimed compositions. *Atlas Powder Co. v E.I. du Pont de Nemours & Co.*, 750 F2d 1569, 224 U.S.P.Q. 409 (Fed. Cir. 1984); Manual of Patent Examining Procedure §2111.03 (6th ed. 1997).

In the present instance, the claims as amended encompass aerosolized compositions comprising non-encapsulated cyclosporine and the use of such compositions for prevention of graft rejection, pulmonary inflammation and/or inhibition of the immune response associated with T-cell mediated immune disorders using such compositions.

In contrast, the Waldrep, Gilbert and Knight references only disclose compositions comprising liposomal encapsulated cyclosporine. Applicants assert that the encapsulation of cyclosporine into liposomes would materially alter the characteristics of Applicant's claimed compositions and methods. Liposome encapsulated cyclosporine would have altered pharmacokinetic properties as compared to non-encapsulated formulations of cyclosporine. For example, because liposomes resemble cell membranes in their structure and composition, the delivery of a liposome encapsulated drug into a cell would be expected to occur as a fusion event between the cell membrane and the liposome membrane resulting in the transfer of the drug into the cell. Clearly, compositions such as Applicants, in which the cyclosporine is non-encapsulated, could not enter the cell via a membrane fusion event.

Therefore, given the differences between the cited references and the present invention, the references cannot anticipate the present invention and the rejection under 35 U.S.C. § 102(b) should be withdrawn.

2. THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 1-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Adjei and Waldrep et al. (U.S. Patent 5,956,378; "Waldrep"), in view of Gilbert, Knight et al. (U.S. Patent 5,049,388) and Applicant's admission on the record. According to the Examiner Adjei, Waldrep, Gilbert, Knight and Applicant admit on the record that the claimed compounds are old and well known in combination with various pharmaceutical carriers and excipients in a dosage form. According to the Examiner, these medicaments are thought as useful for treating graft rejection, inflammation and those conditions claimed and disclosed by Applicant.

A finding of obviousness under §103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the difference between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere,* 383 U.S.1, (1996). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. In *re: O'Farrell,* 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Circ. 1988). In addition, "one way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of unexpected results", *In re Soni*, 54 F. 3d 746, 34 U.S.P.Q. 2d 1684 (Fed.

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Cir. 1995).

In the present instance, the relevant inquiry is whether any of the cited references suggest compositions of non-encapsulated aerosolized cyclosporine and their use for prevention of graft rejection, pulmonary inflammation and/or inhibition of the immune response associated with T-cell mediated immune disorders.

A review of the Waldrep, Gilbert and Knight references reveals that each of the references only disclose compositions comprising liposomal encapsulated cyclosporine. Applicants assert that one of ordinary skill in the art would recognize that liposomal formulations containing cyclosporine would have altered pharmacokinetic properties, such as biodistribution, clearance rates, and toxicity as compared to non-encapsulated formulations of cyclosporine. In this regard, the Examiner's attention is invited to column 2, lines 5-7, of the Knight reference cited by the Examiner which states the following: " in laboratory animals the use of liposomes actually reduced toxic effects observed with the drug alone." However, Applicants have demonstrated, unexpectedly, that doses of non-encapsulated cyclosporine as high as 300 mg per day are tolerated by the treated patient as demonstrated by the working examples presented in the specification (Example 6, p.22-28 of the specification). Indeed, the disclosure of Knight would seem to teach away from Applicants' claimed invention, further indicia of non-obviousness. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F. 2d 443, 230 U.S.P.Q. 416 (Fed. Cir. 1986)

Thus, the mere disclosure of liposomal formulations of cyclosporine would fail to suggest the claimed methods and compositions of the invention, *i.e.*, non-encapsulated

formulations of cyclosporine, nor provide any expectation that the claimed methods utilizing such compositions could successfully be practiced.

In addition, although Adjei discloses compositions of non-encapsulated cyclosporine, Adjei fails to disclose or suggest that such non-encapsulated compositions could be successfully used to prevent graft rejection, pulmonary inflammation and/or inhibition of the immune response associated with T-cell mediated immune disorders using such compositions. Further, this deficiency in the teaching of Adjei is not remedied by any of the additionally cited references.

In summary, Adjei and Waldrep, in combination with Gilbert and Knight, fail to suggest the compositions of the claimed invention or provide a reasonable expectation of success in the use of such compositions for prevention of graft rejection, pulmonary inflammation and/or inhibition of the immune response associated with T-cell mediated immune disorders. Applicants respectfully request, therefore, that the rejections under 35 U.S.C. §103 be withdrawn.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Applicant believes that the invention described

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and defined by the claims is patentable. Withdrawal of all rejections and consideration of the new claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

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APPENDIX

IN THE CLAIMS:

Please amend the claims as follows:

--- 19. (amended) A method for prevention of graft rejection in a lung transplant recipient comprising administering to the recipient directly following transplantation an aerosolized composition [consisting essentially of] comprising :

(i) a dose of non-encapsulated cyclosporine in an amount effective to prevent graft rejection;

(ii) and a propellant.

20. (amended) A method for prevention of graft rejection in a lung transplant recipient comprising administering to the recipient directly following transplantation an aerosolized composition [consisting essentially of] comprising :

(i) a dose of non-encapsulated cyclosporine in an amount effective to prevent graft rejection;

(ii) a dry powder; and

(iii) a propellant.

21. (amended) A method for prevention of graft rejection in a lung transplant recipient comprising administering to the recipient directly following transplantation an aerosolized composition [consisting essentially of] comprising :

(i) a dose of non-encapsulated cyclosporine in an amount effective to prevent graft rejection;

(ii) an organic solvent; and

(iii) a propellant.

25. (amended) A method for ameliorating pulmonary inflammation in a subject comprising administering to the subject an aerosolized composition [consisting essentially of] comprising:

(i) a dose of non-encapsulated cyclosporine in an amount effective to inhibit or ameliorate pulmonary inflammation; and

(ii) a propellant.

26. (amended) A method for ameliorating pulmonary inflammation in a subject comprising administering to the subject an aerosolized composition [consisting essentially of] comprising:

(i) a dose of non-encapsulated cyclosporine in an amount effective to inhibit or ameliorate pulmonary inflammation;

(ii) a dry powder; and

(iii) a propellant.

27. (amended) A method for ameliorating pulmonary inflammation in a subject

comprising administering to the subject an aerosolized composition [consisting essentially of] comprising:

(i) a dose of non-encapsulated cyclosporine effective to inhibit or ameliorate pulmonary inflammation;

(ii) an organic solvent; and

(iii) a propellant.

30. (amended) A method for prevention of graft rejection in a non-lung transplant recipient comprising administering to the non-lung transplant recipient an aerosolized composition [consisting essentially of] comprising:

(i) a dose of non-encapsulated cyclosporine in an amount effective to prevent graft rejection;

(ii) and a propellant.

31. (New) A method for prevention of graft rejection in a non-lung transplant recipient comprising administering to the non-lung transplant recipient an aerosolized composition [consisting essentially of] comprising:

(i) a dose of non-encapsulated cyclosporine in an amount effective to prevent graft rejection;

(ii) a dry powder; and

(iii) and a propellant.

32. (amended) A method for prevention of graft rejection in a non-lung transplant recipient comprising administering to the non-lung transplant recipient an aerosolized composition [consisting essentially of] comprising:

(i) a dose of non-encapsulated cyclosporine in an amount effective to prevent graft rejection;

(ii) an organic solvent; and

(ii) and a propellant.

33. (amended) A method for inhibiting the immune response associated with a T-cell mediated immune disorder in a subject comprising administering to the non-lung transplant recipient an aerosolized composition [consisting essentially of] comprising:

(i) a dose of cyclosporine in an amount effective to inhibit the immune response associated with a T-cell mediated immune disorder; and

(ii) a propellant.

36. (amended) A method for inhibiting the immune response associated with a T-cell mediated immune disorder in a subject comprising administering to the non-lung transplant recipient an aerosolized composition [consisting essentially of] comprising:

(i) a dose of non-encapsulated cyclosporine in an amount effective to

inhibit the immune response associated with a T-cell mediated immune disorder;

(ii) a dry powder; and

(iii) a propellant.

37. (amended) A method for inhibiting the immune response associated with a T-cell mediated immune disorder in a subject comprising administering to the non-lung transplant recipient an aerosolized composition [consisting essentially of] comprising:

(i) a dose of non-encapsulated cyclosporine in an amount effective to inhibit immune response associated with a T-cell mediated immune disorder;

(ii) an organic solvent; and

(iii) a propellant.

38. (amended) An aerosolized composition consisting essentially of:

(i) non-encapsulated cyclosporine in a dose effective to reduce pulmonary inflammation in subjects having pulmonary disorders; and

(ii) a propellant.

39. (amended) An aerosolized composition consisting essentially of :

(i) non-encapsulated cyclosporine in a dose effective to reduce pulmonary inflammation in subjects having pulmonary disorders;

(ii) a dry powder; and

(iii) a propellant.

40. (amended) An aerosolized composition consisting essentially of :

(i) non-encapsulated cyclosporine in doses effective to reduce pulmonary inflammation in subjects having pulmonary disorders;

(ii) an organic solvent; and

(ii) a propellant.

44. (amended) An aerosolized composition consisting essentially of :

(i) non-encapsulated cyclosporine in doses effective to prevent development of an immune response that would lead to graft rejection in a transplant recipient; and

(ii) a propellant.

45. (amended) An aerosolized composition consisting essentially of :

(i) non-encapsulated cyclosporine in a dose sufficient to prevent development of an immune response that would lead to graft

rejection in a transplant recipient;

(ii) a dry powder; and

(iii) a propellant.

46. (amended) An aerosolized composition consisting essentially of :

(i) non-encapsulated cyclosporine in a dose sufficient to prevent development of an immune response that would lead to graft rejection in a transplant recipient;

(ii) an organic solvent; and

(ii) a propellant.